REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-10, 12 and 16-17 are pending. Non-elected claims 4-9 and 16 were withdrawn from consideration by the Examiner.

Consideration of the Information Disclosure Statement being submitted herewith is requested, along with return of an initialed copy of the attached Form PTO-1449.

An inventors' declaration and abstract are submitted herewith to comply with the Examiner's requirements. Entry of the substitute specification is requested (clean and marked-up copies are attached).

Review by the Examiner of the enclosed Figures 4-17 (cited in Example 5 which is added in the substitute specification) and their approval are also requested. Upon the approval of Figs. 4-17, formal drawings will be submitted to the Official Draftsperson.

Essential Matter/Substitute Specification

While the orthogonal self-deconvoluting technique of WO 97/42216 is a convenient way of rapidly and graphically accessing results, it is by no means the only way of deconvoluting mixtures of compounds as recited in claim 1 c). Sheer brute computing power will do the job just as effectively albeit less elegantly. To restrict the invention to any single method of data manipulation would not be commensurate with Applicants' contribution to the art, which is the realization that kinase determinations can be run in stepped libraries of substrate mixtures without needing to separate unmodified from modified species, or their right to claim "the subject matter which the applicant regards as his invention." 35 U.S.C. § 112.

Because as explained above, the orthogonal deconvolution procedure is not an essential feature of the invention, simply citing their earlier-filed patent applications is believed to be adequate by Applicants to satisfy Section 112, first paragraph. But to assist a succinct appreciation of the claimed invention and to satisfy the Examiner's requirement, the relevant disclosure of WO 97/42216 has been added as Example 5 for

inclusion in the specification. No new material has been added, although certain superfluous passages have been deleted and other adaptations have been made.

35 U.S.C. 112 – Enablement

Claims 1-3 and 10-15 were rejected under Section 112, first paragraph, because it was alleged that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." Applicants traverse.

The claims have been restricted to protein kinase enzymes which phosphorylate a substrate molecule at a Ser, Thr or Tyr residue, which the Examiner indicated on page 6 of the Action as being enabled. With this amendment, it is believed that the practice of the invention as regards the composition of the mixtures of putative substrates, their phosphorylation, and their manipulation is enabled by the present specification.

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 112 – Definiteness

Claims 1-3 and 10-15 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

In claim 1, the term "preferably" has been deleted. New claim 17 has been added as a dependent claim and is directed to this deleted subject matter.

Claim 11 has been deleted.

Claim 12 has been amended to address the Examiner's objection to the lack of an upper limit of the number of invariant residues.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1-3 and 10-15 were rejected under Section 102(a) as allegedly being anticipated by Quibell et al. (WO 97/42216). Applicants traverse.

The Examiner's contention that the "foreign priority filing date papers" cannot be relied upon is not understood. The subject matter of this application must be described in the priority document. Here, the claims of priority document GB9722818.3 are largely co-terminous with the claims as filed in the PCT application and under examination in the United States. Admittedly some exemplification was added to Int'l Patent Appln. No. PCT/US98/03259, but this was not "essential matter" nor was Applicants' concept of the invention changed. Even if arguendo the deconvolution process of WO 97/42216 was to be regarded as an essential element of the invention (which Applicants dispute), the priority document was filed with the text of WO 97/42216 as an appendix in order to provided continuity of disclosure. If this rejection is maintained, the Examiner is urged to substantiate what is meant by her objection and to indicate with particularity in what aspects the priority document does not satisfy Section 112 for the present claims.

Furthermore Applicants note that the present claims specifically include sub-libraries of mixtures where the modifiable residue is held fixed. This feature of the invention is not disclosed in Quibell et al. Therefore, the claimed invention is novel over the cited reference.

Claims 1-3 and 10-15 were rejected under Section 102(b) as allegedly anticipated by Patel et al. (WO 96/23813). Applicants traverse.

Although Patel et al. appear to be addressing a similar technique as the presently claimed invention at a superficial level, it should be noted that there are differences. The libraries employed by Patel et al. comprise polypeptides linked to solid phase beads,

that is each bead comprise bears a unique polypeptide (see page 26, line 5, to page 33, line 6, of WO 96/23813). The mixtures of Patel et al. are thus mixtures of beads, each of which represents a pure polypeptide. Note in particular that when Patel et al. "hit" upon a substrate, the relevant individual bead is physically separated by fluorescence activated cell sorting. The beads (including those in the walk libraries at page 30 et seq. of WO 96/23813) are tagged with a unique DNA sequence which is extracted from individual, separated beads and sequenced to determine the sequence of the active (and purified by separation) polypeptide. In contrast, the sub-libraries of Applicants' invention comprise mixtures of compounds in solution and the hit substrates are determined within the mixtures without separation of the phosphorylated substrates from inactive non-phosphorylated substrates.

The non-separation feature has already been recited in claim 1, but the amended claim 1 now clarifies that the substrate molecules of the library are in solution. There is no literal antecedence for the word "solution" in the specification as filed, but it is clear from the examples that the sub-libraries of the present invention are not attached to a solid phase during the assay. Solution phase has a number of advantages over solid phase in relation to the accessibility of the substrate to the enzyme. Patel et al. noted that the proximity of the bead to the active site of the substrate produces undesirable effects and produces difficult noise-to-signal anomalies (see page 31, line 15, of WO 96/23813). The solid phase "mixtures" of Patel et al. also require a very complex set of technologies for single bead separation, nucleotide extraction, and sequencing to get any information from their hits.

At a more subtle level, it should also be noted that the present invention seeks to show the pattern of preferences for phosphorylation of specified amino acid residues in a substrate by a protein kinase enzyme. In contrast, the techniques of Patel et al. seek to understand the binding patterns of SH2 domains which recognize phosphorylated proteins and which then trigger other biological responses, one of which is feedback inhibition of phosphorylation by protein kinase enzymes. This is why, for example, that the walk libraries of Patel et al. each use a phosphotyrosine as the fixed residue. Now

that the claims are restricted to kinase mapping, it will be apparent that Patel et al. is even further removed from the present invention and does not destroy its novelty.

Withdrawal of the Section 102 rejections is requested because all limitations of the claimed invention are not disclosed by the cited references.

Conclusion

Having fully responded to all of the pending objections and rejections contained in the Office Action (Paper No. 11), Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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